American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Oliver Wendell Holmes reading his famous paper on "Childbed Fever." Latest of Series "Pioneers of American Medicine."

Since 1825 *July 1946*

American Journal of Pharmacy

Published monthly by the Philadelphia College of Pharmacy and Science
43d Street, Kingsessing and Woodland Avenues, Philadelphia 4, Pa.

Annual Subscription, $3.00 — Foreign Postage, 25 Cents Extra
Single Numbers, 30 Cents — Back Numbers, 50 Cents

Entered as Second-Class Matter March 27, 1937, at the Post Office at Philadelphia, Pa.
Under Act of March 3, 1879

In the materia medica of modern endocrine therapy

ESTINYL

Schering's introduction of ESTINYL (ethinyl estradiol) was a landmark in estrogen therapy, for ESTINYL is not only a derivative of the ovarian follicular hormone, alpha-estradiol, but is also one of the most potent oral estrogens known today. Administration of extremely small doses results in prompt control of estrogen-deficiency states with noticeably few toxic reactions. Economy is appreciable.

ESTINYL is prescribed in the menopause, in the endocrine treatment of carcinoma of the prostate and as an adjunct to chemotherapy in the treatment of juvenile vaginitis. ESTINYL also is effective substitution therapy for sexual infantilism (hypogonadism) and is of value in the treatment of senile vaginitis and senile pruritus vulvae.

ESTINYL, ethinyl estradiol, in tablets of 0.02 mg. and 0.05 mg. for oral administration; bottles of 100, 250 and 1000.

Trade-Mark ESTINYL—Reg. U. S. Pat. Off.

Schering CORPORATION · BLOOMFIELD · NEW JERSEY
In Canada, Schering Corporation Limited, Montreal

to combat

the depression of

chronic organic disease Many patients with chronic organic disease—arthritis or asthma, for example—sink into a persistent depression characterized by discouragement, or even despair. Unless effectively combated, this depression may handicap management of the basic disorder and intensify its symptoms.

By restoring optimism and interest in useful living, Benzedrine Sulfate frequently helps to overcome prolonged depression accompanying chronic illness. Obviously, in such cases, careful observation of the patient is desirable; and the physician will distinguish between the casual case of low spirits and a true mental depression.

benzedrine sulfate (*racemic amphetamine sulfate, S.K.F.*) Tablets and Elixir

Smith, Kline & French Laboratories, *Philadelphia, Pa.*

AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

Vol. 118. JULY, 1946 No. 7

CONTENTS

E D I T O R I A L

LATIN AMERICAN RELATIONS

CONSIDERABLE attention is being given the potential drug market in South America by manufacturers in the United States. Surveys have shown that a very sizable volume of business in the field of medicinals is possible if this market is developed in the proper way. The war undermined, and in many cases totally destroyed, the commerce in drugs which had been carefully and successfully promoted by several European countries, notably Germany, and this vacuum was filled in part by drugs coming from the United States. We should not expect this relatively easy process of filling a vacuum to continue and already signs are manifest that we must give serious thought to the problem if this opportunity of trade with our southern neighbors is not to be lost.

A number of very positive factors are in our favor, a few of which may be of interest. The old concept of German superiority in the field of synthetics has been shattered by the performance of our chemical industries during the war and with the discovery by Latin Americans that American drugs were just as pure and potent as those long sold by German firms. The increased popularity of the United States Pharmacopoeia in South America in its Spanish translation makes the distribution and use of U. S. P. drugs much more simple in this area. An announcement has already been made that the U. S. P. XIII will be issued in a Spanish edition, a policy of considerable value to our manufacturers. A third and very important influence is the increasing number of students who come to the United States for pharmaceutical study. This is the result of wartime restrictions in European travel and now that the trend of students coming to the States has developed it should be encouraged. Nothing could be more conducive to inter-American friendship and good will than an exchange of students. Every student who comes here from another country invariably becomes an ambassador of good will for us at home. As such he or she is worth a dozen government hirelings who so often do more harm than good. It is unfortunate that more student exchange does not take place but the efforts of our State Department

to encourage this movement are commendable. Our own students should be urged to visit countries in South America and arrange for resident study in some of their outstanding universities.

In our relations with Latin America we have made some serious errors, avoided by the Germans and English much to their credit. First, we as Americans are too much inclined through ignorance to consider South America as a wilderness and its people uneducated and uncultured. We overlook the fact that music, art and literature flourished there when most of our large cities were cow pastures or forests.

Our insistence that the citizens of these countries speak English when they visit here is not matched by an equal effort to speak Spanish or Portuguese when we visit there and yet why should we not be required to do so? They teach English in their schools almost as a matter of course and yet we rarely prescribe Spanish in our high schools. What better language could we teach our children in public school than Spanish? Surely not French or German; even Russian would be a better choice than these.

The last and most difficult point for us to appreciate is the difference in the temperament of those from Latin America and the utter futility of trying to make over these people into our pattern and way of looking at things. To try this is not simply to court failure but an almost certain way to earn their permanent dislike. Even our government has learned this bitter lesson as those familiar with events of the past year will recognize. The so-called white paper on Argentina was a fiasco if ever we had one, particularly since it was timed with such an evident effort to influence the Argentines in their elections which should be their own affair.

We should try to understand our neighbors, cooperate with them and never in any way try to force or squeeze them into any commercial, social, economic, or political pattern that we may feel is good for them. Unless this is the keynote of our policy we shall never have that hemispheral solidarity that all of us need and the exchange of goods and services that will benefit every nation.

L. F. Tice

THE SYNERGISTIC ACTION OF DETERGENTS AND SULFAGUANIDINE AND SUCCINYLSULFATHIAZOLE

By Louis Gershenfeld and Jerome F. Sagin

Introduction and Historical Review

IT has been definitely established that sulfonamides are highly effective in the treatment of diseases caused by different bacteria and other micro-organisms. They are widely used, although the mechanism of their action is still obscure (1, 2, 3, 4). On the other hand, the relative inefficiency of these drugs in certain instances is known. The failure of chemotherapy in these cases may be due to several factors, of which the presence of sulfonamide inhibitors is perhaps the most outstanding (5, 6, 7).

It has been shown that the antibacterial effect of sulfonamides can be increased by the addition of other chemotherapeutic agents (8, 9). Osgood (10) suggested the combined use of neoarsphenamine and sulfathiazole in severe infections in man. Neter (11), on the other hand, reported that the combined action of sulfapyridine and optochin hydrochloride upon pneumococci *in vitro* failed to reveal a synergistic effect.

Numerous reports regarding the bacteriostatic and bactericidal effects of synthetic detergents are available. Their direct action on bacteria has been noted (12, 13, 14) and their effects on toxin production by different bacteria (15), on phage and on viruses (16) have been discussed. The synergism exhibited between detergents and disinfectants has received considerable attention (17, 18). While the mechanism of their action is still obscure, many theories have been advanced. Gershenfeld *et al.* (19, 20, 21) have shown the importance of chemical structure and of hydrogen ion concentration in the antibacterial action of the newer detergents. Baker *et al.* (22, 23, 24) studied their action on the metabolism of the cell. Extensive bibliographies are available in the last two papers mentioned.

Petroff and Schain (17) found the Tergitol penetrants effective in increasing the killing power of various well-known antiseptics. Kintz (26) reported quicker recovery of cases of infected wounds of the soft tissues of the face when an azochloramide-Tergitol 4 combination was used. He also employed a sulfanilamide-sodium tetradecyl sulfate combination for the irrigation of septic wounds. Goldberger (30) obtained favorable results in the treatment of localized

infections by the use of sulfonamides and azochloramide, Lugol's iodine or zinc peroxide. Neter (8, 9, 27) reported a definite synergistic action between azochloramide and various sulfonamides on different pathogenic bacteria. This included both *in vivo* and *in vitro* experiments.

This investigation was carried out to note whether the addition of detergents to sulfaguanidine and succinylsulfathiazole would enhance the efficiency of these compounds by facilitating access of the drug to the organisms or by attacking the organisms themselves or by acting upon interfering substances.

Experimental

Materials and Method

1. The detergents used were:

Name	Chemical Composition	Manufacturer
Aerosol O T	Di-octyl sodium sulfosuccinate	American Cyanamide Co.
Tergitol 4 *	Sodium tetradecyl sulfate	Carbide & Carbon Chem. Corp.
Tergitol 4T *	Triethanolamine tetradecyl sulfate	Carbide & Carbon Chem. Corp.
Tergitol 08 **	Sodium octyl sulfate	Carbide & Carbon Chem. Corp.
Triton K-12	Cetyl dimethyl benzyl ammonium chloride	Rohm & Haas Co.

2. The sulfonamides used were:

Sulfanilyl-guanidine .....Sharp & Dohme (300 H 613)
Succinylsulfathiazole .....Sharp & Dohme

3. Accurately prepared 1 per cent solutions of the various detergents in sterile distilled water were used as stock solutions. These were made freshly for each test and examined for sterility.

4. *Technique*

The organisms used in this study were 22-26 hour old cultures of *Eberthella typhosa* (standard F. D. A. strain) and *Escherichia coli.* The test cultures were transplanted daily in F. D. A. broth and stock cultures were kept on 1.5 per cent agar slants.

* Commercial Tergitol 4 and Tergitol 4T have a 25% active ingredient content.

** Tergitol 08 has a 40% active ingredient content.

The culture medium used in the tests was nutrient broth containing 0.3 per cent Liebig's meat extract, 1 per cent Difco Bacto-Peptone, 0.5 per cent sodium chloride and adjusted colorimetrically to pH 7. The broth was tubed in 5 cc. amounts and autoclaved at fifteen pounds pressure for twenty minutes.

Sulfaguanidine and succinylsulfathiazole were dissolved in the broth in the amounts indicated below, tubed in 5 cc. amounts and autoclaved at fifteen pounds pressure for twenty minutes. The detergents were added aseptically to give desired concentrations. Controls for sterility were carried out.

The bacteriostatic activity of these drugs alone and in combination was determined on the basis of inhibition of visible growth. To test for bacteriostasis, four standard loopfuls of all tubes that failed to show growth were transplanted to 10 cc. of F. D. A. broth. Growth after incubation at 37° C. for forty-eight hours indicated bacteriostatic action. A representative experiment was as follows:

Sulfaguanidine was used in concentrations of 1, 10, 100, 200 and 220 mg. per cent.

Succinylsulfathiazole, due to its limited solubility, was used in concentrations of 10, 30 and 50 mg. per cent.

A dilution of the detergent which by itself had no effect on the organisms was used.

Broth without any drugs was used as a control.

The tubes containing 5 cc. of solution were seeded with 0.1 cc. of a suspension of the test organism prepared by centrifuging twenty-four hour cultures and suspending the sedimented cells in a volume of saline solution equal to that of the original culture (10 cc.). This suspension was then diluted with 1:5 saline solution and contained approximately 100,000 organisms per cc. as determined by plate counts. The tubes were then incubated at 37° C. and observed daily for a period of one week.

Results

Experiment 1

The action of sulfaguanidine (1, 10, 100, 200, 220 mg. per cent) and succinylsulfathiazole (10, 30, 50 mg. per cent) on *Eberthella typhosa* was determined at pH 6, 7, and 7.6. Neither drug had any appreciable effects on the organism although sulfaguanidine in higher concentrations (100, 200, 220 mg. per cent) had a slight inhibitory effect. The changes in pH did not affect the action of the drugs.

The following anionic detergents were tested for their effect on the synergistic action with sulfaguanidine and succinylsulfathiazole (concentrations as above):

Aerosol OT	1:500	Tergitol 4T	1:500
Tergitol 4	1:500	Tergitol 08	1:625

These dilutions were used inasmuch as they were found not to inhibit the organism when used alone. No effect on the antibacterial action of either sulfaguanidine or succinylsulfathiazole was noted for either Aerosol OT or Tergitol 4T at any pH. Tergitol 4 and Tergitol 08 showed a definite synergistic effect at pH 6. Inhibition was most pronounced with sulfaguanidine at 100, 200 and 220 mg. per cent. None of the detergents had any appreciable effect on the action of succinylsulfathiazole against *E. typhosa* or *E. coli* at any pH tested. Controls were run containing broth only without any drugs.

Experiment 2

Tergitol 4 (1:100), Tergitol 08 (1:125), Tergitol 4T (1:100) and Aerosol OT (1:100) were tested on sulfaguanidine and succinylsulfathiazole as in Experiment 1. Aerosol OT and Tergitol 4T had no appreciable effect when used alone on the organism or in combination with either sulfonamide. None of the detergents had any effect on the action of succinylsulfathiazole at any pH. The effect of Tergitol 4 and Tergitol 08 is shown in the tables below. No appreciable change occurred at pH 6, 7 or 7.6.

Hours of incubation at 37° C.	Sulfaguanidine mg. % and Tergitol 4 (1:100)					
	0	1	10	100	200	220
24	++	+	+	+	—	—
48	++	+	+	+	—	—
72	++	++	++	+	—	—
96	++	++	++	+	+	—
120	+++	++	++	+	+	—
144	+++	++	++	+	+	—
168	+++	++	++	+	+	—

Hours of incubation at 37° C.	Sulfaguanidine mg. % and Tergitol 08 (1:125)					
	0	1	10	100	200	220
24	++++	+	+	—	—	—
48	++++	++	++	—	—	—
72	++++	+++	+++	—	—	—
96	++++	++++	++++	—	—	—
120	++++	++++	++++	—	—	—
144	++++	++++	++++	+	+	—
168	++++	++++	++++	+	+	—

Experiment 3

The effects of sulfaguanidine and succinylsulfathiazole in concentrations noted in previous experiments alone and in combination with Aerosol OT, Tergitol 4, Tergitol 4T (1:500) and Tergitol 08 (1:625) on *E. coli* were determined at pH 6, 7, 7.6.

The drugs themselves did not inhibit the growth of the organism nor did they when used in combination with the detergents.

Experiment 4

The above experiment was repeated except that the detergents were used in the following concentrations:

Tergitol 4, Tergitol 4T, Aerosol OT (1:100) and Tergitol 08 (1:125)

E. coli was more resistant than *E. typhosa* to the combined action of the drugs even when they were used in high concentrations. None of the detergents had any appreciable effect on the antibacterial action of either sulfonamide. No change in the combined action of the drugs was noted with changes in pH.

Experiment 5

In this experiment the cationic detergent Triton K-12 was tested in a dilution of 1:10,000. Its effect on the antibacterial action of sulfaguanidine and succinylsulfathiazole against *E. typhosa* and *E. coli* was determined. The synergistic effect here was very pronounced, as shown in the following tables:

1. *Action on E. typhosa*

Hours of incubation at 37° C.	Sulfaguanidine mg. %					
	0	1	10	100	200	220
24	++++	++++	++++	+++	++	++
48	++++	++++	++++	+++	++	++
72	++++	++++	++++	+++	+++	+++
96	++++	++++	++++	++++	+++	+++
120	++++	++++	++++	++++	+++	+++
144	++++	++++	++++	++++	+++	+++
168	++++	++++	++++	++++	+++	+++

Hours of incubation at 37° C.	Sulfaguanidine mg. % and Triton K-12 (1:10,000)					
	0	1	10	100	200	220
24	++++	—	—	—	—	—
48	++++	—	—	—	—	—
72	++++	—	—	—	—	—
96	++++	—	—	—	—	—
120	++++	—	—	—	—	—
144	++++	—	—	—	—	—
168	++++	—	—	—	—	—

The detergent itself did not inhibit the growth of the organism. Succinylsulfathiazole (10, 30, 50 mg. per cent) also showed complete inhibition of growth when used in combination with the detergent, but not when used alone.

2. Action on E. coli

Hours of incubation at 37° C.	Sulfaguanidine mg. %					
	0	1	10	100	200	220
24	++++	++++	++++	++	++	++
48	++++	++++	++++	++	++	++
72	++++	++++	++++	+++	++	++
96	++++	++++	++++	+++	+++	+++
120	++++	++++	++++	+++	+++	+++
144	++++	++++	++++	++++	+++	+++
168	++++	++++	++++	++++	++++	++++

Hours of incubation at 37° C.	Sulfaguanidine mg. % and Triton K-12 (1:10,000)					
	0	1	10	100	200	220
24	++++	++++	++++	—	—	—
48	++++	++++	++++	—	—	—
72	++++	++++	++++	—	—	—
96	++++	++++	++++	—	—	—
120	++++	++++	++++	—	—	—
144	++++	++++	++++	—	—	—
168	++++	++++	++++	—	—	—

The detergent when used by itself did not inhibit the growth of the organism.

Succinylsulfathiazole (10, 30 and 50 mg. per cent) when used in combination with the detergent inhibited the growth of the organism very slightly.

Discussion

These experiments indicate that there is a definite *in vitro* synergistic action in the concentrations studied between the detergents Tergitol 4, Tergitol 08 and Triton K-12 and sulfaguanidine against *Eberthella typhosa* and *Escherichia coli.* Succinylsulfathiazole was affected only by the cationic detergent Triton K-12. The combined action of these drugs over a pH range of 6, 7 and 7.6 would seem to confirm the findings of Gershenfeld *et al.* (20) that the hydrogen-ion concentration is an important factor when dealing with detergents. The property of surface tension reduction appears to be independent of the bacteriostatic properties of the detergents (19). Theoretically the reduction in surface tension should make the cell more penetrable, but the difference in findings with Aerosol OT, Triton K-12, Tergitol

4, Tergitol 4T and Tergitol 08 is due in all probability to differences in their chemical structures (19).

While the mechanism of the synergistic action between detergents and sulfonamides has not been definitely established, findings reported here would seem to indicate that if non toxic, they may have a definite role in sulfonamide chemotherapy, especially for use in localized conditions on the intestinal mucosa.

Summary

Sterility tests and *in vitro* bacteriostatic tests were carried out using the following detergents in the concentrations mentioned:

Aerosol OT .....1:500 and 1:100
Tergitol 4 .....1:500 and 1:100
Tergitol 4T .....1:500 and 1:100
Tergitol 08 .....1:625 and 1:125
Triton K-12 .....1:10,000

These concentrations were found to have no effect *in vitro* on *Eberthella typhosa* and *Escherichia coli.*

The effect of sulfaguanidine (1, 10, 100, 200 and 220 mg. per cent) and succinylsulfathiazole (10, 30 and 50 mg. per cent) on *E. typhosa* and *E. coli* were determined *in vitro.*

In vitro tests were then carried out to determine the effects of the detergents listed above on the antibacterial action of sulfaganidine and succinylsulfathiazole in the concentrations listed above. The effect of changes in pH (6, 7 and 7.6) was also noted.

Conclusions

1. Sulfaguanidine (1, 10, 100, 200, 220 mg. per cent) and succinylsulfathiazole (10, 30, 50 mg. per cent) do not inhibit either *E. typhosa* or *E. coli in vitro* under conditions reported in this investigation.

2. Aerosol OT (1:500 and 1:100) and Tergitol 4T (1:500 and 1:100) have no effect on the antibacterial action of the two sulfonamides studied.

3. Tergitol 4 (1:500 and 1:100) and Tergitol 08 (1:625 and 1:125), both anionic detergents, have a definite synergistic effect on the action of sulfaguanidine (in the concentrations studied) against *E. typhosa.*

4. The cationic detergent Triton K-12 (1:10,000) has a marked synergistic effect on the action of both sulfaguanidine and succinylsulfathiazole against *E. typhosa* and *E. coli.*

5. Sulfaguanidine alone and in combination with the detergents studied was found generally superior to succinylsulfathiazole against *E. typhosa* and *E. coli.*

BIBLIOGRAPHY

1. Bliss and Long: *Bull. Johns Hopkins Hosp., 69*:14 (1941).
2. Harris and Kohn: *J. Pharmacol. & Exp. Therap., 73*:384 (1941).
3. Sapeika: *S. African Med., 15*:185 (1941).
4. Schmelkes *et al.*: *Proc. Soc. Exp. Biol. & Med., 50*:145 (1942).
5. Neter: *Proc. Soc. Exp. Biol. & Med., 43*:52 (1940).
6. Wyss: *Proc. Soc. Exp. Biol. & Med., 48*:222 (1941).
7. Strauss *et al.*: *J. Immunol., 42*:3, 313 (1941).
8. Neter: *J. Pharmacol. & Exp. Therap., 74*:1 (1942).
9. Neter: *Proc. Soc. Exp. Biol. & Med., 47*:303 (1941).
10. Osgood *et al.*: *Amer. J. Med. Sciences, 200*:596 (1940).
11. Neter: *J. Bact., 41*:273 (1941).
13. Freedlander: *Proc. Soc. Exp. Biol. & Med., 44*:51 (1940).
14. Gershenfeld and Perlstein: *Amer. J. Pharm., 113*:89 (1941).
15. Caryl: *Ind. & Eng. Chem., 33*:731 (1941).
16. Bayliss and Halvorsan: *J. Bact., 29*:9 (1935).
17. Petroff and Schain: *Quart. Bull. Sea View Hosp.* (July, 1940).
18. Gershenfeld and Witlin: *Amer. J. Pharm., 113*:215 (1941).
19. Gershenfeld and Milanick: *Amer. J. Pharm., 113*:306 (1941).
20. Gershenfeld and Perlstein: *Amer. J. Pharm., 113*:237 (1941).
21. Gershenfeld and Ibsen: *Amer. J. Pharm., 114*:281 (1942).
22. Baker *et al.*: *J. Exp. Med., 73*:249 (1941).
23. Baker *et al.*: *J. Exp. Med., 74*:621 (1941).
24. Baker and Miller: *Science, 91*:624 (1940).
25. Aerosol Wetting Agents: Am. Cyanamid & Chem. Corp. N. Y. (1941).
26. Kintz: *The Military Surgeon, 89*:1 (1941).
27. Neter: *Amer. J. Surg., 48*:69 (1942).
28. Schmelkes and Wyss: *J. Bact.* (January, 1942).
29. Synthetic Wetting Agents and Detergents: Rohm & Haas (1940).
30. Goldberger: *Amer. J. Surg., 56*:353 (1942).

THE USES AND LIMITATIONS OF DE-IONIZED WATER FOR PHARMACEUTICAL PURPOSES*

By W. S. Morrison **

THE American pharmaceutical manufacturers have shown interest in the development of the cation exchange resins which are capable of adsorbing metallic ions, and the resinous materials which adsorb acid from solutions, since the announcement of the original work in England ten years ago. As evidence of this interest, Mr. R. L. Brault's report of February 4, 1946, indicated that of 23 pharmaceutical manufacturers replying to his survey, 11 firms used the de-ionizing resins for the procurement of pharmaceutical water, that one firm used de-mineralized water, and that 11 firms were using single distillation for the preparation of mechanically produced water for their specific requirements. In 1942, at Denver, Colorado, Dr. R. J. Myers of the Resinous Products Company of Philadelphia presented a paper before the Scientific Section of the American Pharmaceutical Association which summarized the preliminary investigations of resinous exchange studies on various hard waters, and he noted the chemical composition of mineral-free water as it was obtained from ion exchange units operating in several sections of the country. A suggested use of such treated water was made for pharmaceutical purposes and it is the intent of this paper to present the recent de-ionizing developments which further recommend this method of producing mineral-free water for almost all pharmaceutical purposes.

The principle of de-ionization is one of chemical exchange and adsorption carried out in a two step cycle. For the purposes of this discussion, the first of these steps can be considered as being one carried out in the presence of an insoluble granular resin whose molecular structure contains nuclear sulfonic acid molecules, the hydrogen of which is replaceable for metallic cations. In the treatment of water, the objectionable ions of calcium, magnesium, and sodium are drawn into the lattice structure of the large resinous molecule with the release of an equivalent number of hydrogen ions. The hydrogen

* Presented at the meeting of the American Pharmaceutical Manufacturers' Association, June 12, 1946.

** Research Director, Illinois Water Treatment Company.

ions, thus liberated, unite with the anions of the split salt to form their equivalent acid.

In the second step, a polymerized amine formaldehyde resin is used to remove the mineral acids formed in the first step. These acids, which appear as the result of the breaking up of salts in the hydrogen exchange reaction, are removed as whole molecules in step two. An exhausted resin, that is one no longer capable of hydrogen exchange on acid adsorption, is regenerated by flushing dilute hydrochloric or sulfuric acid through the cation exchanger and a dilute solution of sodium carbonate or sodium hydroxide through the acid adsorbing medium. The characteristic of the exchangers to conform to the law of mass action in reversing the equilibria by utilizing higher concentrations of acid or alkali during regenerations, produces cyclic performance. Each cycle, therefore, comprises an exhaustion and a regeneration of the ion exchangers.

The composition of raw water varies a great deal according to the sections in which it is pumped, and often times there is great divergence within the same locality. Some manufacturing processes are further complicated by having one water supply which in itself will show seasonal variations. These factors usually render raw water unsuitable for pharmaceutical purposes. De-ionizing produces on such supplies a water free of dissolved solids which is the equal of, and often considerably better than, single distilled water in so far as total solids are concerned. This mineral-free water costs but a fraction of that produced by steam stills, and it is supplied under line pressure in volumes that would be, from a cost standpoint, prohibitive to distill. The mineral-free water is supplied to the pharmacist at the same temperature of the raw supply. In general, then, the de-ionizing resinous exchangers eliminate a variable water condition which, in turn, is important in maintaining pharmaceutical product stability. Experience in twenty plants shows that pharmaceutical processes thus governed are able to maintain uniformity of clarity, color, and taste by employing low solid, mineral-free water.

While it is true that the quality of many products has been benefited by de-ionized water and that costs have been reduced in operations where large volumes of water are needed, it is only fair to state that some limitations were observed in the early exchangers. Their troublesome factors have been thoroughly investigated and new resins formulated to overcome the objection of the earlier ion

exchange materials. The objection of color throw, observed during intermittent operation of the exchanger in the de-ionized effluent, is almost entirely eliminated by using nuclear sulfonic acid groups in the hydrogen resin base. The presence of "amines" is now completely eliminated in the effluent by employing a more completely C stage polymerized amine formaldehyde resin for acid adsorption.

Heretofore, the use of de-ionizing resins has been confined to a low, close temperature range. This limitation has been overcome in the course of resin improvement, and there are now available exchangers which permit the treatment of water up to 160° F., with the possibility of still higher temperatures being permissible in the near future. It is now possible to recirculate hot water in ampul washing equipment.

Possibly the chief limitation of the exchange phenomenon has been in its inability to remove silica from natural raw water. There is no doubt that the scope of de-ionizing has been narrowed by the fact that any silica in the reactions remains unexchanged.

In those few pharmaceutical processes where it is deemed necessary, silica can now be removed by the use of sodium fluoride ahead of the hydrogen exchange reactor. The sodium fluoride is converted to hydrogen fluoride in the first stage which then converts silica to fluosilicic acid, which is adsorbed with the other mineral acids of the reaction on the acid binding resin in stage two. De-ionized effluents also will contain some dissolved carbon dioxide as any carbonates in the natural water will have been converted to carbonic acid which, to a large degree, passes through as a solution of carbon dioxide. The amount is dependent on the carbonate content of the raw supply. If this carbon dioxide content is objectionable, it may be eliminated to a degree which is governed by requirement. Aeration will bring it down to a low residual, but if it must be brought to as near zero as possible, this can be accomplished by degassifying under vacuum.

Natural water containing organic color or colloidal suspended matter may require coagulation and filtration prior to de-ionizing treatment. This is particularly true of waters containing spectrophotometer haze values of 1 to 3. Data collected on surface water so treated shows spectrophotometer color less than one and zero haze values. With this limitation corrected, it has been shown that the ion exchange process is equal to that of distillation for general pharmaceutical use. It is not to be presumed, however, that all limitations

have as yet been corrected. Water containing pyrogens, for example, cannot be passed through the exchangers to obtain complete pyrogen removal. Conversely, however, water free of these complex bodies is not contaminated in the reaction of ion exchange. It is essential that water to be used in parenteral solutions be fed to steam stills from a de-ionizing unit to procure, by single distillation, a water the quality of which will meet the exacting standard of the pharmacopoeia.

The resins are normally housed in vertical cylindrical pressure tanks. To insure the treated water's passing uniformly through the bed so that all parts of the resin are utilized equally, water is introduced at the top of the tank and collected at the bottom by a system of piping called distributors. To prevent the loss of resin through the lower distributor and to aid in the equal flow of the water through the bed, the resins are supported by several layers of pure quartz gravel ranging from coarse at the bottom to fine at the top.

In addition to the tank, provision is made for water connections at top and bottom and for controlling the flow of water as an injection system for regenerant solution. This may be done with a series of individual valves, by the same valves remote controlled from a central location; or, more usually, by a single multiport valve, which in itself controls the phases of regeneration. Naturally, the tanks themselves, the distributors, piping, and valves must all be resistant to the corrosive action of the dilute acids encountered, not only to prevent destruction of the equipment but to protect the purity of the treated water. Freedom from corrosion is obtained by fabricating of materials inherently resistant to the acids or by lining steel with acid proof materials such as plastic or rubber.

In addition to the actual reactor tanks there must be suitable tanks for holding the proper regenerant solutions and methods of introducing them into the resin beds in the proper concentrations. The latter may be done by pumping or by the use of a hydraulic ejector. Minimum mechanical requirements for the production of pure de-ionized water also include meters for measuring the quantity of water treated as well as its purity. In some cases means must be provided for dispelling CO_2 and hence raising the pH. Where large volumes of water are required intermittently, a storage tank and pump eliminate the need of much larger equipment.

Storage tanks are essential in those installations requiring 24 hour a day production to carry over the regeneration period, or the

entire equipment built in duplicate so that one set of tanks is operated while the other is down for regeneration.

Where the raw water contains appreciable magnesium, a sodium zeolite water softener is provided to supply magnesium free water for making up soda ash solutions as well as providing softened water for the actual regeneration of the acid adsorbing resin. This is done to eliminate the precipitation of $Mg(OH)_2$ on the bed, lengthening the rinse period of regeneration. Water from the cationic exchanger could be used, but the use of the softener permits the exchanger to be regenerated at the same time and also eliminates the use of some of the capacity of the cationic exchanger.

The capacity of the equipment is a function of the amount of resin in the tanks with an inherent capacity for each cubic foot, and the concentration of solids in the water being treated. Thus, a given amount of resin may have a capacity on a certain water to treat 10,000 gallons before it is regenerated and on a water containing 1/10 the solids it will treat 100,000 gallons between regenerations. The length of time between regenerations will depend, of course, upon the rate, whether 10,000 or 100,000 gallons are used.

It is true that ion exchange processes have been largely accepted for water treatment purposes; however, these materials are becoming increasingly important in specialized fields. Applications of the removal of ionizable substances, or the substitution of ions, offer the chemist new tools in the research laboratory. At the Frederick J. Stearns Company in Detroit it has been noted that protein hydrolyzate solutions can be passed through the ion exchange materials for the selective adsorption of non-essential amino acids. Glutamic and aspartic acids are readily adsorbed from such solutions, thereby obtaining the essential amino acids free of these interfering substances.

A researcher in the field, Mr. R. J. Block, states that he has been able to use successfully ion exchange materials in a process for the production of arginine, histidine, and lysine. Pharmaceutical research conducted by others demonstrates that thiamine hydrochloride can be quantitatively adsorbed by cation exchange. Also in organic solution studies new methods have been found for the purification of sugar juice. Considerable emphasis has been placed on this subject during the present critical sugar shortage and the results indicate that ash, which consists of calcium and magnesium salts in the raw cane sugar juice, can be removed by ionic exchange which reduces the

number of steps in the refinery for the production of cane sugar. Higher yields of sugar are being obtained with edible molasses as one of the by-products of the process. The field of ionic exchange opens many roads and opportunities for research. Many of the problems that have been presented are not solved, but each case is exploratory and the results are indicative of what may be investigated.

	Resin Exchanger Before Reaction		Salt in Water Being Treated		Insoluble Resin Salt Formed	Compound Remaining in Treated Water	
CATION-EXCHANGE RESIN							
Sodium Cycle	$2NaR$	+	$CaSO_4$	=	CaR_2	Na_2SO_4	CO_2
	$2NaR$	+	$MgCl_2$	=	MgR_2	$2NaCl$	
	$2NaR$	+	$Ca(HCO_3)_2$	=	CaR_2	$2NaHCO_3$	
Hydrogen Cycle	$2HR$	+	$CaSO_4$	=	CaR_2	H_2SO_4	
	$2HR$	+	$MgCl_2$	=	MgR_2	$2HCl$	
	$2HR$	+	$Ca(HCO_3)_2$	=	CaR_2	H_2O	
	HR	+	$NaCl$	=	NaR	HCl	
ANION-EXCHANGE RESIN							
Acid Removal	RX	+	H_2SO_4	=	$(RX).H_2SO_4$	No residual dissolved substances	
	RX	+	HCl	=	$RX.HCl$		

RX —Anion-exchange resin such as Amberlite IR-4 with the acid binding substituent X.

NaR—Sodium salt of cation-exchange resin, such as Amberlite IR-1 in sodium cycle.

HR —Hydrogen derivative of cation-exchange resin, such as Amberlite IR-1 in hydrogen cycle.

THE SITUATION IN SWITZERLAND WITH REGARD TO PHARMACEUTICAL SPECIALTIES

Editor's Note—The following article was submitted in original form by Novavita Aktiengesellschaft of Zurich. It is an excellent summary of the Swiss treatment of pharmaceutical specialties.

PHARMACEUTICAL specialties were started in Switzerland at the beginning of this century. At that time Swiss industry began to be interested in the manufacture of standard-medicaments, and to produce and distribute these as branded articles for the most usual prescriptions. However, only German and French manufacturers were interested at first and started to consider the Swiss market. Especially the dye industry of the said two countries became aware of the possibility of bringing ready-made medicaments to the market. The co-operation between the industry and the professors of hospitals became closer and closer, as the latter knew that the industry possessed the possibility of carrying through great tests in the therapeutic sphere. Little by little, this was extended to the whole apothecary prescription, and there is hardly any prescription at present for which there is not available a ready-made pharmaceutical specialty.

The Swiss dye-industry did not hesitate to take up this branch and did not spare any efforts to carry through its development on a serious scientific basis. It is to be said here that Switzerland has a world-wide reputation in regard to pharmaceutical specialties, and there is hardly any country in the whole world where pharmaceutical specialties of Swiss origin are not available.

The Swiss national industry, thanks to its work and production, enjoys the full confidence of Swiss hospitals and the medical profession. Besides specialties of Swiss origin, those of German and French origin are very much used too in Switzerland. The manufacturers in these countries have always given their full attention to the Swiss market and are, therefore, still very well represented here. Some of these important firms have their own representatives in Switzerland, whereas the greatest part of them have entrusted good Swiss firms with their representation. The American pharmaceutical industry is practically not represented in Switzerland. Only one important American firm, and this through its English branch, has

treated the Swiss market, where respectable returns were received. Switzerland is a country of tourists with the corresponding industry of greatest importance. All efforts are made in Switzerland to offer to foreign visitors every kind of comfort, and this is the reason why in all pharmacies and drug-stores of big centres or health-resorts frequented by foreigners, certain American specialties can be found. It is to be said, however, that these American specialties are in general bought only by American people who are spending their vacations here, whereas the said products have almost never been offered to the Swiss public.

There are two categories of pharmaceutical specialties, namely:

1st. Purely scientific therapeutic preparations, which are distributed only to physicians or hospitals.

2nd. Medicaments which are directly sold to the public, i. e. the consumer, as standardized articles.

It is impossible to carry through both kinds of advertising for one product, as the physicians do not prescribe specialties which are sold directly to the public.

The sale of medicaments in Switzerland is classified in different categories:

a) Specialties which contain narcotics and which are, therefore, subject to the Swiss law regarding narcotics. Such medicaments can be sold by pharmacies only on the prescription of a physician (this prescription cannot be renewed).

b) Specialties containing drugs or chemicals of great potency, which can be sold by pharmacies only on a medical prescription.

c) Specialties of more harmless nature, which can be sold by pharmacies and drugstores.

d) Specialties for external application, of absolutely harmless nature, which can be sold everywhere and by every shop of the branch.

Every specialty which is sold in Switzerland is subject to a license of the Intercantonal Control-Office for the Approbation of Medicaments at Berne. Licenses are given only to Swiss Agents who take the responsibility for eventual harm which could result from such specialties. Original packages with all literature and eventual advertisements must be submitted to the said Intercantonal Con-

trol-Office. The advertising of specialties directly to the public shall not be quackery, it shall not contain any superlatives and shall not be too verbose.

Packaging

This may be in English, but it has to contain literature in German and French, and if possible, in Italian as well. This is sufficient for the beginning, but packaging with German and French imprinting shall be created later on.

Import Charges

The import of pharmaceutical specialties is free and without any restriction in Switzerland, subject to license for sale by the Intercantonal Control-Office. For the said license, a fee of about sfr. 120.— to 150.— is to be paid as per specialty, for controlling and testing. The import-duty is sfrs. 100.— as per 100 Kgs. (gross weight). Switzerland knows only duty on the weight and not on the value. If the specialty contains alcohol, a special monopoly-fee is to be paid, as follows:

under 20 degrees of alcohol content.....	Fr. 50.—	per 100 Kgs.
from 20 to and including 75 degrees of alcohol content	Fr. 200.—	per 100 Kgs.
over 75 degrees of alcohol content.....	Fr. 300.—	per 100 Kgs. (gross weight)

Discount-Rates

The pharmacist demands a discount of at least 40 per cent on the selling-price, for prescription specialties, whereas the minimum profit of the retailer (pharmacist or druggist) is 33 1/3 per cent on the selling-price of retail-specialties. The wholesaler demands a minimum discount of 15 per cent on the cost-price to the pharmacist or druggist. If payment is made within 30 days, the supplier allows the retailer a discount of 2-3 per cent.

Price-Control

There is a Federal Price-Control-Office, to which every price must be submitted, if the article in question has not been in the market before the 1st September of 1939. Prices of specialties which

were in the market before the said date, cannot be increased without consulting the said Price-Control-Office and without having the consent of same.

Turnover Tax

The whole turnover is subject to a tax, which is paid by the consumer. Carrying through imports of foreign specialties, the Custom authorities charge sfrs. 33.— per 100 Kgs. (gross weight) on account of turnover tax. The corresponding amount can be deducted by the importer from his quarterly account with the Federal Revenue Office, so that this tax is neither charged to the manufacturer abroad, nor to the importer. The turnover tax is added to the retailers' price, so that it is practically paid by the consumer.

Luxury Tax

This tax is charged only to perfumery-articles, but not to pharmaceutical specialties.

Advertising

Pharmaceutical specialties are advertised in Switzerland by two different methods, the one of which excludes the other.

1st. Advertising to Physicians

Physicians are informed by sending them literature, in order to distribute purely scientific therapeutic products. A card asking for samples is very often enclosed with the said literature, so that the physician has the possibility of asking for samples free of charge. This advertising is assisted by advertisement in the professional periodicals. In Switzerland, there are at least three of these which must be considered, i. e.

"Schweizerische Medizinische Wochenschrift" (Swiss Weekly Medical Journal)
"Die Praxis" (The Practice)
"Schweizerische Aerztezeitung" (Physicians' Review of Switzerland)

All these journals are issued in two languages (French and German) and are well-known all over Switzerland.

The most effective advertising consists in the visiting of physicians by a special detail man for this purpose, who should possess, if possible, an academic degree and should already be introduced to medical circles. The detailer has to discuss with the physician the specialty made by the firm he represents, and he has to discuss the advantages and the new effect of the said specialty. He has to accept orders for samples, but not for deliveries of merchandise. The most important work of a detailer is to visit the hospitals, where his greatest and most difficult duty consists in inducing the staff to publish recommendations of the product. It is possible to attain such a publication, only if the specialty represents an innovation and if its effect takes place in a new way. Swiss professors and physicians are extremely reserved with regard to publications, for which they have to give their name. It is one of the most difficult things to attain such a publication for a pharmaceutical specialty. It is almost impossible to attain a so-called paid publication, with the sole exception of a professor allowing a medical student to make up a publication against recompense. However, in such a case the professor signs the treatise with his own name and only allows publication of the same if the specialty in question is really worth while.

Sick Fund

The greatest part of the population of Switzerland are members of a sick fund. There are certain districts where 95 per cent of the population are members. In many districts, membership is a compulsory measure of the State for persons having under a certain minimum income. The physician has only a limited possibility of prescribing with regard to patients of a sick fund, as these funds, i. e. their concordate, has made up a list of specialties which are allowed for the sick-funds' practice. It is extremely difficult to get a specialty on this list, because only 2 or 3 specialties are allowed for each prescription. New specialties, which do not represent any therapeutic innovation and improvement compared with the existing ones, have no chance to be admitted to the list. The specialties which are admitted by the sick fund are subject to a commission of University professors in the towns of Zurich, Bâle, Berne, Lausanne and Geneva. It is, therefore, very difficult to induce all these professors to accede to the admission to the list of sick-funds' specialties. A specialty which is not admitted to the said list, can only be prescribed by the

physician to patients who are not members of sick funds and who, therefore, have to pay for the medicament themselves. This is the reason why the possibility of prescribing such specialties is very limited for the physician, and consequently, the sale of these products is considerably reduced. The price of the specialties is also of great importance with regard to their admission to sick funds, as the commission in question does not admit exorbitant prices. Sick funds protect as far as possible analogous articles, as they are in general considerably cheaper than the original specialties.

2nd. Advertising to Laymen

This kind of advertising is more appropriate for specialties of a wide prescription-sphere, in case a product cannot appeal on the basis of scientific proof. For carrying through advertising to laymen, it is necessary to get the consent of the Intercantonal Control-Office for the Approbation of Medicaments at Berne, to which all literature and advertisements, as well as placards, that is to say, all printed matter, must be submitted. The texts which are admitted by this Control-Office can be distributed as advertisements in the newspapers, or as literature. The cheapest way of advertising is always that of newspapers, although this is relatively expensive in Switzerland. This small country has four different languages, i. e. German, French, Italian and Romanic. The latter population also speaks German or Italian. The advertising by newspaper therefore necessary in two languages at least, namely French and German. In Switzerland, there is only one fortnightly review with a circulation of 400,000, the next one being a weekly review with a circulation of 130,000, and then a daily newspaper with 115,000. All other periodicals have smaller circulations. There is only one daily newspaper appearing in 3 editions and can be considered as the most important and most prominent newspaper of the country. There are no other newspapers of other than local nature. All illustrated magazines have editions under 100,000, but they are very well edited, and the advertisements very well placed. Prices of advertisements are very high, because of the small editions.

Retailers like to make up nice and attractive window-dressing, but they often demand a monthly rent of sfrs. 10.— to sfrs. 30.— and more. Windows of pharmacies and drugstores are well and carefully dressed in Switzerland. In the smallest places of the province

there are found drugstores with great and beautiful windows, as if they were in the center of great towns. Advertising is highly effective, if newspaper advertisement and window-display correspond with each other.

Solvency of Customers

The pharmacies and drugstores in Switzerland are very good and solvent customers. Both professions are very well situated, and from time to time, they are competing with each other to the quick. At present, they are just quarreling for business reasons. A good representative knows the few insolvent firms of the said two categories and will not deliver merchandise to them, or only on condition that payment is made on delivery. Therefore, the *del credere* or risk of loss is not to be estimated very high.

Representation

In Switzerland there is a great number of agencies, with many years' practice in the matter. They are very well known to the customers and possess a good staff of representatives. It is very important for American firms to make a careful choice of their agents within the branch. The population of Switzerland is very conservative and has certain peculiarities. The methods of foreign countries are very often unknown in Switzerland, or they are a hindrance to the development. It is of greatest importance, therefore, that an agent be able to inform the American manufacturer about all details through his own experience. If the agent does not know his branch very well, he should first go through an apprenticeship for which the foreign manufacturer should have to pay. The owner of an important English factory was recently in Switzerland in order to look for representatives. He expressly declared that his trip to Switzerland was worth while, as the written offers of agents which he had received from Switzerland had to be refused after detailed examination in the country.

The agent takes charge of the merchandise, either on his own account, or on commission. In general, the manufacturer abroad has to do whatever is necessary with regard to advertising in Switzerland. It will be difficult to find an agent who is willing to carry through advertising on his own cost.

In general, the agent takes possession of the merchandise at the frontier. He effects the clearance and submits the calculations to the manufacturer. The foreign manufacturer and the Swiss agent together fix the selling prices for wholesale dealers, retailers and the public. The agent's commission in Switzerland is between 20 per cent and 40 per cent of the selling price to the retailer. If the agent has to carry through advertising, 40 per cent will not be sufficient. The provision rate between 20 per cent and 40 per cent depends from the risks which the agent in Switzerland has to enter.

It depends upon the viewpoint, whether a great or small firm shall be entrusted with representations in Switzerland, as a representative of smaller performance has less products to represent, whereas a great agency has other advantages.

The American Chamber of Commerce in Switzerland will furnish every manufacturer in America with further details regarding the product he wishes to export to Switzerland, or which he intends to import to his country.

SELECTED ABSTRACTS

Methyl-Thiouracil and Thiouracil as Antithyroid Drugs. G. E. Glock. *Brit. J. Pharmacol. and Chemother. 1,* 127 (1946). The antithyroid activities of 4-methyl-2-thiouracil and 2-thiouracil were compared by feeding the drugs to young rats for 100 days. The two drugs produced approximately the same inhibition of growth and the same depression in metabolic rate.

Histological studies revealed that methyl-thiouracil produces considerably less thyroid enlargement and mascularity than thiouracil. It is emphasized, however, that thyroid size should not be taken as a criterion of antithyroid activity. Metabolic rate determinations are essential.

Metabolism studies carried out on rats after 23 weeks of a diet containing one or the other of the drugs showed that approximately 62 per cent of methyl-thiouracil and 72 per cent of thiouracil is excreted in the urine.

Both drugs produced changes in organs other than the thyroid in rats which had been on the diet for 100 days. In both groups of animals the anterior pituitary was found to show changes identical with or closely similar to those seen after thyroidectomy. Rats treated with methyl-thiouracil were found to be sexually very immature.

The author advocates the use of methyl-thiouracil in the treatment of human thyrotoxicosis. Several references to published clinical observations on this drug are given.

Synthetic Substitutes for Quinidine. G. S. Dawes. *Brit. J. Pharmacol. and Chemother. 1,* 90 (1946). The quinidine-like activity of 45 compounds was studied by means of a method in which the reduction in the maximal rate at which the isolated rabbit auricle will respond to stimulation is determined. In addition to quinidine, niquidine and numerous synthetic compounds somewhat related in structure to these, the group of drugs investigated included some which are local anesthetics or which structurally closely resemble some of the

sympathomimetic amines, *viz.*, cocaine, procaine, butethanol, butyn, syntropan, trasentin, pethidine and phenacaine. Papaverine and sparteine were also studied.

It was observed that a number of the local anesthetics and spasmolytics possessed quinidine-like properties when tested by the method described. The most promising synthetic substitute for quinidine found was a benzilic ester of piperidino-ethanol. This compound was 5.4 times as active as quinidine and had a therapeutic efficiency index three to six times that of the latter when injected into mice, intravenously or intraperitoneally, respectively.

The relationship existing between structure and quinidine-like activity is discussed. The most active compounds possessed aromatic and basic groups joined by ester, ether, keto or carbinol linkages. Increased activity was found to be associated, within certain limits, with increased lipoid solubility and increase in the size of the alkyl group attached to the basic nitrogen atom.

It was noted that the quaternary salts of very active tertiary compounds are quite inactive, suggesting that the active component of a solution is the free base (which can penetrate the cell membrane) rather than the cation (which is believed to act at the cell surface). Curariform and atropine-like properties appear to be characteristic of the cation.

Curare as an Aid to the Anesthetist. H. H. Griffith. *Lancet 249,* 74 (1945); through *Quart. J. Pharm. & Pharmacol. 19,* 82 (1946). The use of the curare preparation "Intocostrin" by expert anesthetists is stated to produce with cyclopropane anesthesia relaxation similar to that obtainable with spinal anesthesia. The dosage of curare recommended for an adult is 60 to 100 mg. (3 to 5 ml. of Intocostrin), administered intravenously; this may be repeated.

The drug may also be used in conjunction with ether anesthesia, or when ether is given with cyclopropane, ethylene or nitrous oxide; in these cases the dosage of Intocostrin should be reduced to 2 ml. It may also be employed to reinforce the action of pentothal, and when the relaxation produced by spinal anesthesia is wearing off too soon, provided that the sensibility of the patient is obtained by hypnotics or a "sleeping dose" of a general anesthetic.

Investigations on the Autoxidation of Diethyl Ether. Part II. Autoxidation Products and the Autoxidation Process. F. Reimers. *Quart. J. Pharm. & Pharmacol. 19, 27* (1946). Employing methods for the analysis of the autoxidation products of ether described in a previous paper, the author reports experimental data to refute the theories of Wieland and Wingler and of Rieche and Meister regarding the genesis of the various products which have been identified in deteriorated samples of ether. Complete analyses were performed on approximately 8,000 samples of ether which had been stored under various conditions.

Although the author is unable to advance a scheme explaining the autoxidation of ether, he has made a noteworthy contribution to this subject. During the autoxidation of ether neither vinyl ether nor hydrogen peroxide is formed. Vinyl ethers are not hydrolyzed in ether, even if the latter contains water. Free acetaldehyde, acetic acid and small quantities of formic acid are formed by the splitting of the ether peroxide which forms in closed ampuls until all of the oxygen contained in ether has been consumed. On analysis ether peroxide was found to yield 1 mol. of acetaldehyde + 1 mol. of hydrogen peroxide.

Natural ether peroxide is shown not to be identical with either the "*bis*-hydroxyethyl peroxide" or "α-hydroxyethyl hydrogen peroxide" synthesized by other investigators. The author concludes that the autoxidation of ether produces a peroxide which always has the same composition and properties, and that the process is a chain reaction with very long reaction chains. It is conjectured that autoxidation is induced by the activation of an ether molecule; the latter splits, forming free radicals which react with oxygen in such a way that free radicals are again formed, by means of which the chain of oxidations is continued.

The addition of an antoxidant, such as 0.01 per cent pyrogallol, *p*-phenylenediamine or phenyl-α-naphthylamine, to samples of ether free from oxygen but containing peroxide prevented the formation of free acetaldehyde. On the other hand, the ether peroxide in control samples to which no antoxidant was added underwent partial splitting.

The results of polarographic studies will be presented in a later paper.

Potentiation of Insulin Hypoglycaemia by Nicotinyltaurine (β-Nicotinamidoethanesulfonic Acid). A. A. Goldberg and H. S. Jefferies. *Quart. J. Pharm. & Pharmacol. 19,* 48 (1946). Nicotinyltaurine was prepared by the interaction of nicotinylchloride hydrochloride and taurine; it is a white crystalline substance possessing both lipophilic and hydrophilic properties. Its aqueous solution is strongly acid, but the solution of the sodium salt is neutral and is suitable for either oral or parenteral administration.

The investigation of its property of potentiating insulin arose from previously published observations that taurine is an insulin synergist and that nicotinamide influences the blood sugar level in both normal and diabetic subjects.

Ten ml. of the solution of sodium nicotinamidoethanesulfonate were introduced into the stomach of the lightly anesthetized rabbit by means of a soft rubber catheter. The insulin was administered subcutaneously two hours later. It was observed that an oral dose of 10 to 25 mg./Kg. of the potentiator together with 0.5 I. U./Kg. of insulin produced a drop in the blood sugar level comparable to that caused by 1.0 I. U./Kg. of insulin alone.

Subcutaneous administration of the drug to mice showed it to have very low toxicity. Similar studies were also made on nicotinamide, taurine, nikethamide (nicotinic diethylamide) and the sodium salt of nicotinic acid.

The Low Therapeutic Activity of Penicillin K Relative to That of Penicillins F, G, and X, and Its Pharmacological Basis. H. Eagle and A. Musselman. *Science 103,* 618 (1946). Data are presented to show that penicillin K disappears from the blood, and presumably the tissue fluids as well, much more rapidly than do penicillins F, G or X. One hour after the injection into rabbits or man of penicillins F, G, K and X at a dosage of 0.6 mg./Kg., the blood levels of K were only one-eleventh to one-fourth of those of the other penicillins.

The average recovery of K from the urine of both rabbits and man was 30-35 per cent. In contrast, the recovery of F, G and X averaged 74 per cent in rabbits and 91 per cent in man.

A pure preparation of K was found to be one-eleventh as active as G, and one-thirtieth as active as X, in the treatment of experimental streptococcal infections in mice.

These observations suggest that penicillin K is inactivated in the body to a greater extent and more rapidly than is the case with F, G or X. This would result in lower therapeutic activity than would be expected from its *in vitro* activity.

The authors state that the Q-176 strain of *Penicillium chrysogenum* is the one most widely used at the present time for the commercial production of penicillin, and that up to 50 per cent of the penicillins produced by this strain in the absence of specific precursor substances may be penicillin K. The ordinary dosage of such a product may therefore be therapeutically inadequate.

It is recommended that the method of production of penicillin be modified in order to minimize the proportion of K in the commercial product. If a penicillin consisting of a single molecular species of F, G or X cannot be provided, it would be desirable to select some means of standardization which has a more direct relationship to therapeutic activity than the determination of bactericidal activity *in vitro*. The use of experimental animals for the determination of either therapeutic activity or residual blood penicillin is suggested for this purpose.

An Intestinal Antiseptic: 2-Sulfanilamido-5-Carboxythiazole. P. S. Winnek. *Science 103,* 719 (1946). 2-Sulfanilamido-5-carboxythiazole is a white, crystalline compound, the synthesis of which was first described in 1942. It is a fairly strong acid, liberating carbon dioxide from sodium bicarbonate. Its solubility in water at room temperature is approximately 40 mg. per cent, the pH of the saturated solution being 3.2. The mono- and disodium salts are soluble in water to an extent greater than 30 per cent; the pH values are 5.4 and 8.5, respectively. The sodium salt of the acetyl derivative has a solubility of about 8 per cent, the pH being 5.4 for the saturated solution.

In vitro studies of 2-sulfanilamido-5-carboxythiazole led to the conclusion that it possessed as much activity against *Streptococcus* (C203) as sulfanilamide, sulfadiazine and sulfaguanidine. Its antipneumococcic activity was comparable to that of sulfanilamide and sulfadiazine, but slightly less than that of sulfapyridine and sulfaguanidine. Against *Staphylococcus aureus* it was much more active

than sulfanilamide, but far less so than sulfathiazole. Against the enteric group of organisms it was generally more active than sulfanilamide and sulfaguanidine, and in some cases equal to sulfapyridine, sulfathiazole and sulfadiazine.

Acute toxicity studies demonstrated that the LD_{50} for mice was 8.0 gm./Kg. (oral), 5.0-6.0 gm./Kg. (intraperitoneal), 8.0 gm./Kg. (subcutaneous). In mice, rabbits and dogs the chronic toxicity was comparable with that of succinylsulfathiazole, and much less than that of sulfaguanidine and the readily absorbed sulfonamides.

The maximum blood level of the drug observed in man was less than 1.0 mg. per cent, following the oral administration of 0.25 gm./Kg. per day for five days. Excretion studies in man indicated that from 3 to 11 per cent (average, 6.1 per cent) of the drug was excreted in the urine.

2-Sulfanilamido-5-carboxythiazole was found to reduce the number of *E. coli* in the feces of dogs and man more rapidly and at a lower dose level than other investigators have reported for either succinylsulfathiazole or phthalylsulfathiazole. This observation is in general agreement with a report published by other workers of clinical studies in which 2-sulfanilamido-5-carboxythiazole was used to treat bacillary dysentery.

Extensive clinical trials are now in progress to evaluate the compound with respect to other drugs used for intestinal antisepsis.

BOOK REVIEWS

German for the Scientist. Peter F. Wiener. xii + 238 pages. Chemical Publishing Company, 1946. Price: $3.50.

The book has a good selection of modern German scientific publications. It contains a condensation of grammar to give the advanced science student a reading knowledge of German. Although the author's intention is good, it is impossible to make a difficult language so simple. The German language has an extended cultural background. It is a difficult tongue for the English speaking student. Moreover, German scientists are highly educated people. They do not express their thoughts in simple constructions. Most of them had their education in the German "Gymnasium" with Latin and Greek as the predominant languages. For this reason, their sentences are even more complicated than those in the average language. The author has an excellent command of both languages. His translations are very good. However, he does not realize the language difficulties of the average science student.

Languages were not formed according to grammar. Studying grammar is a necessary evil for everybody who cannot think in another language. The English speaking student has to learn to analyze complicated constructions in order to understand the correct meaning. He will never be able to do this without good training in grammar. He has to be sure that he can never go wrong. Furthermore, the use of the dictionary should be explained. The author's hint on compounds (page 6) is not sufficient for that purpose.

The scientist who has to read German texts is primarily interested in his subject. A reading knowledge does not mean "that at first one should be satisfied to gather merely the general meaning of a paragraph. It is much better to cover as much ground as possible than to produce perfect translations" (Foreword, by Paul Spoerri). A scientist must have a sufficient knowledge of German to use it as a tool to increase his knowledge in his field. In science accuracy is absolutely necessary. One letter may change the whole meaning of a text. Therefore, I cannot agree with the author who thinks that the

declension of adjectives is negligible. How can a student understand the difference between "eine leichte lösliche Verbindung" and "eine leicht lösliche Verbindung" without knowing the adjective endings?

The following good explanations are worth mentioning: The suffixes "hin" and "her," the infinitive with "zu" (page 14), the relative and reflexive pronouns (pages 21, 22), the participial construction (page 22), the artificial subject "es" (page 22). With the exception of "Tln." (which can only be used in the dative plur.), the list of abbreviations is correct. Most science readers do not always give them accurately.

When the author tries to simplify the German grammar, he is not accurate. A few inaccuracies may be mentioned:

Page 1: "All nouns, or words used as nouns, as are, at times infinitives and neuter adjectives, begin with a capital letter." Every German adjective can also be used as a masculine or feminine noun.

Page 8: "All intransitive verbs expressing motion are constructed with 'sein' in German." The author forgot the verbs expressing change of conditions.

Page 13: "In ordinary sentences containing these verbs (separable verbs) the prefix is put at the end." This statement is only correct for sentences in the present and past tenses.

Page 15: "But nouns ending in el, en, er never change the ending in the plural." This is not correct in the case of feminine nouns ending in er (Schwester, Feder).

Page 30: The example "grosser Mann" for declension is a common error in elementary German grammars. There are only a few expressions in German as well as in English that can be used without the article in the singular. Nobody can say "mit grossem Mann" (with tall man), or "Ich sehe grossen Mann" (I see tall man).

Pages 34, 35: The subjunctive of irregular verbs in the active voice is omitted. The difference between "geworden" and "worden" is not explained (cf. page 9).

Page 40: The meanings given for prepositions are rather superficial. "bei" near by, "gegen" against, "über" over or across are not correct.

There are many misprints in the book, especially in appendix V. I mention the most important errors.

Page 19: jetzt sind die Lichte am helsten (read Lichter am hellsten).

Page 44: Reaction (read Reaktion); spez. Gew. 1.19 (read 1, 19); filtrirt (read filtriert); extrahirt (read extrahiert).

Page 45: destillirt (read destilliert); Aktivier-ungsenergie (read Aktivie-rungsenergie).

Page 46: Widerstand-sänderung (read Widerstands-änderung); abges-tossenen (read abge-stossenen); Gesch-windigkeit (read Geschwindigkeit).

Page 47: in Spiel (read im Spiel).

Page 48: diese Gleichgewicht (read dieses Gleichgewicht); characteristische (read charakteristische).

Page 130: Die Analyse von Kristallen mit den Roentgen-Strahlen —(read dem Röntgenstrahlen—) Spektrometer.

W. Reuning.

Air Cargo Potential in Drugs and Pharmaceuticals. By Spencer A. Larsen and William Reitz. Wayne University Press, Detroit, 1946.

Forward looking industrialists will be interested in this extensive survey of the estimated future of air transportation in the field of drugs and pharmaceuticals. The study represents the third of a series under the guidance of the School of Business Administration, Wayne University and sponsored by a group of important manufacturing concerns including two major airlines. The report is clearly written with a minimum of methodology and a maximum of conclusions and trends. There seems little doubt that air transportation of cargo, although now a lusty infant, is rapidly growing into an important influence in the transportation field.

Environmental Warmth and Its Measurement. By T. Bedford, D. Sc., Ph. D., M. I. Min. E. Published by His Majesty's Stationery Office, London, and Distributed by the British Information Services, 30 Rockefeller Plaza, New York. Price: 25¢.

During the war it became evident that living and working conditions on many battleships had become so poor that the efficiency of the crew was greatly impaired. With great increase in heat producing machinery, crowding and warfare in the tropics, conditions that were never good became intolerable.

The problem in brief became "What is the ratio of space allocated to the human element to the space allocated to the mechanical element of the total fighting machine (ship plus ship's company) which will make it the most efficient engine of war?"

This book is one of reference prepared for the Royal Naval Personnel Research Committee of the Medical Research Council based on studies conducted by their Habitability Sub-Committee.

Many industries having a similar problem of workmen trying to perform efficiently under conditions of high temperature and humidity will find this a most useful report on the measurement of conditions and their interpretation.

Available also are charts for the Calculation of Environmental Warmth at 45¢. These charts reduce the calculations needed in determining humidity, air velocities, radiation, etc., and their interrelationships in producing effective temperature.

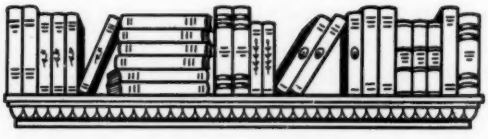
The Science and Art of Perfumery. By Edward Sagarin. 268 pages incl. index. McGraw-Hill, New York, 1946. Price: $3.00.

This is a short but very interesting book by an author who is able to write authoritatively on the subject by reason of his long association with the industry. It is written in a free and easily read style so that one need not be an expert or even a chemist in order to appreciate and understand fully its contents. In fact it is almost what might be called a popular treatise.

The book is divided into seventeen chapters and two appendices. The first part is largely historical but not the dry type of historical

coverage frequently seen in more scientific treatises. The chapters which follow by their very titles intrigue the reader as do those of a serial article or those of some adventure story. For example, we find "The Perfumes That Nature Created," "An Artist in a Laboratory," "Children of Aphrodite" and "Living in a Perfumed World."

Those who expect to find in this book processes of organic synthesis and complicated chemical data will be disappointed but for all those to whom perfumery is occasionally a problem and those who like their science simplified, this book will prove not only of value but very good and pleasant reading.



NEW! CREAMALIN* NOW IN *capsules*

New form preferred by many patients

Supplied in convenient pocket or purse size

Ideal for patients on sugar restricted diet

Attractive
COUNTER DISPLAY
(2 dozen boxes of 24's
Pocket or purse size)

For many years, CREAMALIN (Brand of Aluminum Hydroxide Gel) has been used in cases of peptic ulcer and gastric hyperacidity as an effective antacid. It has brought untold relief to sufferers who have used Creamalin in its several forms: liquid (unflavored, flavored, highly flavored, and with mineral oil) and tablets. Many users have expressed a preference for capsules. Thus, we now offer this new convenient form in boxes of 24 (especially designed for vest pocket or purse) and in bottles of 100.

Ask your wholesaler or your Winthrop representative for details.

*Trademark Reg. U. S. Pat. Off.

Complete WINTHROP CATALOG published in 1945-1946 American Druggist Blue Book and Drug Topics Red Book

Winthrop CHEMICAL COMPANY, INC.

Pharmaceuticals of merit for the physician

NEW YORK 13, N. Y. • WINDSOR, ONT.

Introduced under Fair Trade

Report

TO AMERICAN PHARMACISTS

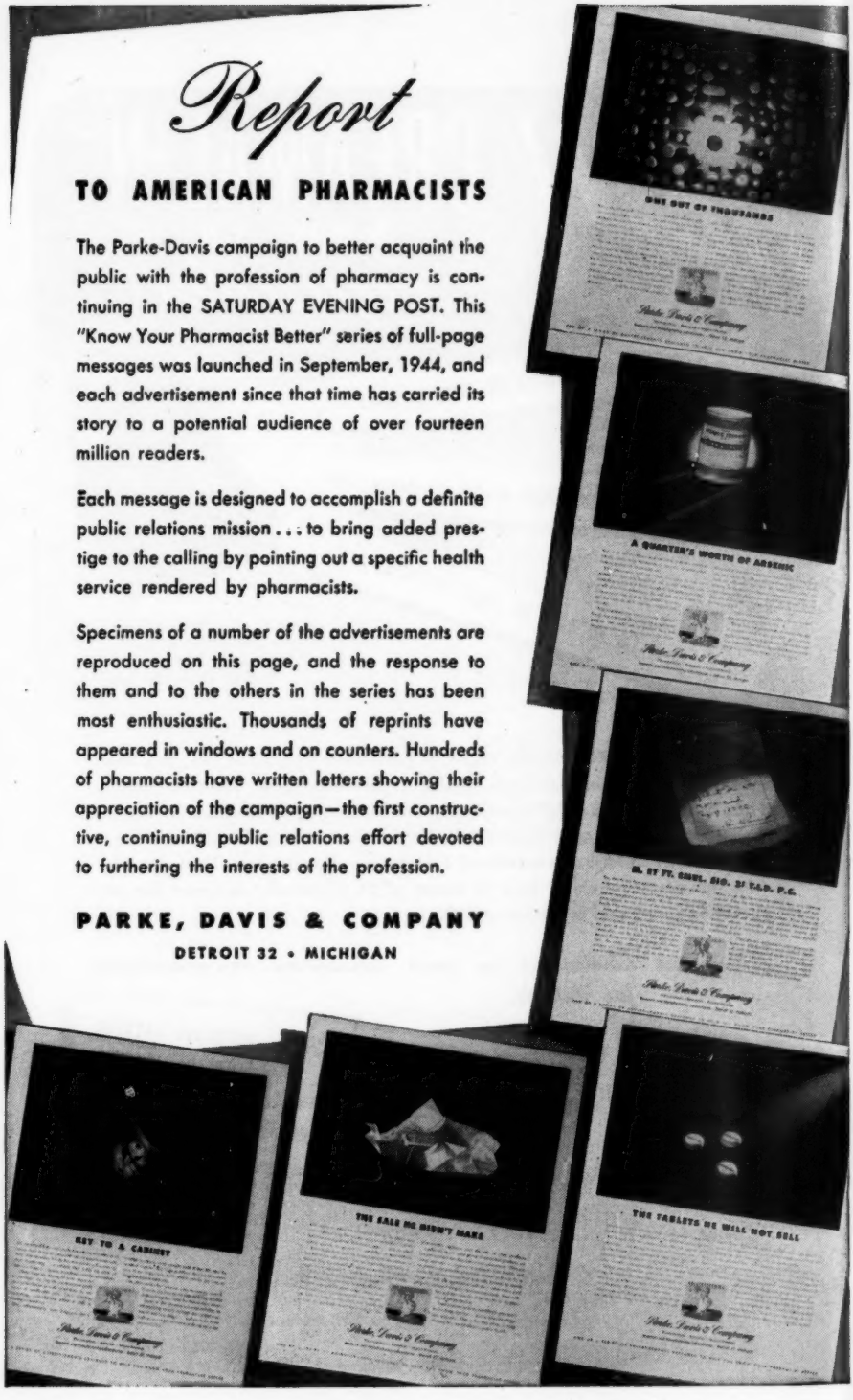
The Parke-Davis campaign to better acquaint the public with the profession of pharmacy is continuing in the SATURDAY EVENING POST. This "Know Your Pharmacist Better" series of full-page messages was launched in September, 1944, and each advertisement since that time has carried its story to a potential audience of over fourteen million readers.

Each message is designed to accomplish a definite public relations mission . . . to bring added prestige to the calling by pointing out a specific health service rendered by pharmacists.

Specimens of a number of the advertisements are reproduced on this page, and the response to them and to the others in the series has been most enthusiastic. Thousands of reprints have appeared in windows and on counters. Hundreds of pharmacists have written letters showing their appreciation of the campaign—the first constructive, continuing public relations effort devoted to furthering the interests of the profession.

PARKE, DAVIS & COMPANY

DETROIT 32 • MICHIGAN



American Journal of Pharmacy

The American Journal of Pharmacy is the oldest continuously published scientific periodical of its kind in America, having been established by the Philadelphia College of Pharmacy in 1825. After the original issue there were three other preliminary numbers until 1829, when regular publication began. From then until 1852 four issues were published annually, with the single exception of 1847, when an additional number appeared. Six issues a year were printed from 1853 to 1870, at which time the Journal became a monthly publication.

Former Editors of the Journal have been: Daniel B. Smith, 1825-1828; Benjamin Ellis, 1829-1831; Robert E. Griffith, 1831-1836; Joseph Carson, 1836-1850; William Procter, Jr., 1850-1871; John M. Maisch, 1871-1893; Henry Trimble, 1893-1898; Henry Kraemer, 1898-1917; George M. Beringer, 1917-1921, and Ivor Griffith, 1921-1941.

Established and maintained as a record of the progress of pharmacy and the allied sciences, the Journal's contents and policies are governed by an Editor and a Committee on Publications elected by the members of the College.

Manuscripts should be sent to the Editor, who does not assume any responsibility in connection with the views or investigations of contributors of accepted manuscripts, other than to exercise general care in selection.

Contributors are allowed a reasonable number of copies of this Journal, free of charge, if applied for when the proof is returned.

Reprints, if desired, should be ordered when the proof is returned. The table below shows the *approximate* cost of reprints, the make-up of the pages to be identically the same as in the Journal. The actual cost may vary from the figures given, and will depend upon the amount of presswork, paper, binding, and other factors. Reprints containing half-tones may be expected to cost somewhat more than the rates given.

	2 pp.	4 pp.	8 pp.	16 pp.
50 copies	$3.50	$6.00	$10.50	$11.25
100 "	4.25	7.00	14.00	15.00
250 "	5.25	9.00	18.75	20.00

Covers with Titles	
50 copies	$ 5.00
100 "	6.50
250 "	10.25